بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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MONA MAGHRABY

Effects of Direct Acting Antivirals on Glomerular Filtration Rates and Neutrophil Gelatinase-Associated Lipocalin during the Treatment of Hepatitis C Patients

Thesis

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in **Internal Medicine**

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Michael George Sami Nada

List of Contents

List of Tables

List of Tables **cont...**

List of Figures

List of Figures **cont...**

List of Abbreviations

Abb.	Full term
ADPKD	Autosomal dominant polycystic kidney disease
AIN	Acute interstitial nephritis
AKI	Acute kidney injury
ALT	Serum alanine aminotransferase
AST	Serum aspartate aminotransferase
ATN	Acute tubular necrosis
CKD	Chronic kidney disease
DAAs	Direct-acting antivirals
DAC	Daclatasvir
ELISA	Enzyme linked immunosorbent assay
FDA	Food and Drug Administration
Fe	Iron
FGN	Fibrillary glomerulonephritis
FSGS	Focal segmental glomerulosclerosis
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRS	Hepatorenal Syndrome
IFN	Interferon
Ig	Immunoglobulins
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IQR	Interquartile range
IRS	Insulin receptor substrate proteins
ITGN	Immunotactoid glomerulonephritis
LRP2	Lipoprotein receptor-related protein 2
MAP	Mitogen activated protein kinase
MI	Myocardial infarction
MMP-9	Matrix metalloproteinase 9
MN	Membranous glomerulonephritis
MPGN	Membranoproliferative glomerulonephritis
MSFI	Migration stimulating factor inhibitor

List of Abbreviations **cont...**

Abb.	Full term
NGAL	Neutrophil gelatinase associated lipocalin
NNPIs	Non-nucleoside polymerase inhibitors
NPIs	Nucleoside polymerase inhibitors
NS	Nonstructural proteins
PAN	Polyarteritis Nodusa
peg-IFN	Pegylated interferon
PIs	Protease inhibitors
RBP	Retinol binding protein
RBV	Ribavirin
RF	Rheumatoid factor
ROC Curve	Receiver Operating Characteristic Curve
SCR	Structurally conserved regions
SD	Standard deviation
SOF	Sofosbuvir
SPSS	Statistical package for Social Science
SR-B1	Scavenger receptor B1
SVR	Sustained viral response
TAPA-1	Target of anitproliferative antibody 1
TGFβ	Transforming Growth factor Beta
TLR	Toll-like receptors
TLR-2	Toll-like receptors
TLR-3	Toll-like receptors
TNF-α	Tumor Necrosis Factor alpha
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

INTRODUCTION

Hepatitis C virus (HCV) infection is a major global health challenge, according to the World Health Organization (WHO) report in 2017, it is estimated that about 71 million people are chronically infected worldwide ***(World Health Organization, 2017).***

Unfortunately, Egypt has one of the highest global burdens of hepatitis C virus (predominantly genotype 4) infections, it is estimated that prevalence of HCV is around 4.5% to 6.7% ***(Doss et al., 2018).***

The ultimate goal of hepatitis C treatment is to reduce the occurrence of end-stage liver disease and its complications, including decompensated cirrhosis, liver transplantation, and Hepatocellular carcinoma (HCC). Initially, chronic hepatitis C was treated by conventional interferon (IFN) monotherapy which yielded very poor response rates. Addition of the guanosine analogue, ribavirin (RBV) to conventional IFN was associated with a slight improvement in sustained viral response (SVR) ***(Suda and Sakamoto, 2015).***

The year 2011 marked the dawn of the new era of direct-acting antivirals (DAAs) for hepatitis C. DAAs were initially introduced as add-ons to the previous standard of care consisting of PEG-IFNα/RBV. In 2014, a breakthrough in HCV therapy was achieved with the introduction of IFN-free -oral

DAAs, with SVR rates in excess of 90% after 12 weeks of therapy ***(Kamal, 2018).***

Concerns on renal safety may represent a limitation to a wide use of DAAs in HCV patients, despite the proven efficacy of this class of drugs. Furthermore, the reported unreliability of conventional markers of renal function in patients with liver cirrhosis can contribute to discourage DAA prescription ***(Levin et al., 2013).***

HCV infection is prevalent in patients with renal impairment, diverse groups of patients with renal disease require consideration when treatment of hepatitis C is indicated. These include patients with chronic kidney disease (CKD) stage 4 (eGFR = 15–29 ml/min/1.73 m2) or those with CKD stage 5 (eGFR <15 ml/min/1.73 m2). Some of these groups, renal function could potentially improve with antiviral treatment. However, organ recovery may be delayed or worsened in others ***(European Association for the Study of the Liver, 2018)***.

In patients with severe renal dysfunction (eGFR <30 ml/min/1.73 m2), the safety of sofosbuvir-based regimens has been questioned. A recommended regimen in HCV genotype 4 is the combination of ritonavir-boosted paritaprevir and ombitasvir for 12 weeks with daily ribavirin (200 mg/day) if the haemoglobin level is >10 g/dl at (Baseline), or safer with

combination of grazoprevir and elbasvir for 12 weeks ***(European Association for the Study of the Liver, 2018).***

Neutrophil gelatinase associated lipocalin (NGAL) is a novel kidney biomarker. It is a small glycoprotein secreted by epithelial cells (liver, kidney, lungs) and some white blood cells (neutrophils, monocytes and macrophages). It's filtered in the glomerulus and reabsorbed by the proximal tubules. It can be measured in blood and urine and so it is used as early marker of acute kidney injury ***(Strazzulla et al., 2018).***